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Strengthening the Case: Prenatal Alcohol Exposure Is Associated With Increased Risk for Conduct Disorder

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What's Known on This Subject

Prenatal alcohol exposure is associated with increased rates of externalizing behaviors; however, the effects of this exposure may be confounded by genetic vulnerability to disinhibitory behavior and/or the effects of cigarette smoking in pregnancy.

What This Study Adds

We address the role of parental substance use diagnoses, as well as parental antisocial diagnoses, on the relationship of low levels of prenatal alcohol intake to later offspring externalizing symptoms, while also controlling for prenatal tobacco exposure.

ABSTRACT

OBJECTIVE. The purpose of this study was to examine the relationship between alcohol exposure in pregnancy and offspring conduct disorder symptoms in adolescence and to examine how much this increasingly known association may be mediated by maternal and paternal externalizing diagnoses, including lifetime maternal and paternal alcohol and drug abuse/dependence diagnoses as well as antisocial disorders. Few other studies have examined the contribution of these diagnoses across both parents.

METHOD. A population sample of 1252 adolescents (53.8% female; drawn from the Minnesota Twin Family Study) as well as both of their parents completed structured diagnostic interviews to generate lifetime psychiatric diagnoses; mothers were also retrospectively interviewed about alcohol and nicotine use during pregnancy. Linear regression models were used to test the effects of prenatal alcohol exposure on adolescents' conduct-disorder symptoms.

RESULTS. Prenatal exposure to alcohol was associated with higher levels of conduct-disorder symptoms in offspring, even after statistically controlling for the effects of parental externalizing disorders (illicit substance use disorders, alcohol dependence, and antisocial/behavioral disorders), prenatal nicotine exposure, monozygosity, gestational age, and birth weight.

CONCLUSIONS. Prenatal alcohol exposure contributes to increased risk for conduct disorder in offspring. *Pediatrics* 2008;122:e1225–e1230

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Key Words

conduct disorder, prenatal alcohol exposure, fetal alcohol effects

Abbreviations

FAS—fetal alcohol syndrome
FASD—fetal alcohol spectrum disorders
APD—antisocial personality disorder
CD—conduct disorder
MTFS—Minnesota Twin Family Study
DSM-III-R—*Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*
AAB—adult antisocial behavior

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APPROXIMATELY 1 IN 5 American women consumes alcohol during pregnancy,¹ despite increasing recognition of alcohol's adverse effects on fetal development, including fetal alcohol syndrome (FAS). FAS accompanies significant prenatal alcohol exposure and is characterized by facial dysmorphism, growth restriction, and central nervous system abnormalities²; however, lesser amounts of prenatal alcohol exposure have also been shown to be associated with adverse psychological and neurodevelopmental outcomes, including deficits in cognitive performance^{3–5} and psychosocial functioning.^{6–8} Fetal alcohol spectrum disorders (FASD) is the umbrella term for this constellation of associated deficits.⁹

Although the deficits in psychosocial functioning seem diffuse, one area of particular concern is the increased rates of externalizing behaviors, such as aggressiveness and delinquency, that are observed among children who are prenatally exposed even to small amounts of alcohol. This association was first noted in studies that used standardized parent questionnaires, such as the Child Behavior Checklist, to examine samples of alcohol-exposed children.^{3,10–12} The pattern of elevated Child Behavior Checklist scores suggested that this population might also be at increased risk for clinically significant impairment (ie, diagnoses of externalizing disorders). In fact, Langbehn and Cadoret¹³ reported that in a sample of ~200 adopted adults, fetal alcohol exposure was associated with increased risk for later antisocial personality disorder (APD). Similarly, Hill et al¹⁴ reported an association between prenatal alcohol exposure and later conduct-disorder (CD) diagnoses in a sample of 150 youth selected for risk for alcoholism.

The authors of these studies, as well as a review by Rutter,¹⁵ have questioned whether the behavioral effects of low levels of prenatal alcohol exposure could be confounded with an inherited vulnerability to disinhibitory behavior. This concern arose from the fact that women who choose to drink in pregnancy are not a randomly selected sample. For instance, women who drink in pregnancy are known to be more likely to have preexisting antisocial or alcohol use disorders^{16–18} as well as indicators of adverse environments such as physical abuse¹⁹ or high levels of psychosocial

stress and low social support.²⁰ In addition, women with antisocial personality or alcohol use disorders may be more likely to select antisocial or alcoholic mates.^{21,22} Both genetic and environmental risks are associated with having antisocial or alcoholic parents and are known to lead to higher prevalence of offspring antisocial disorders.^{23–26}

To address these potentially confounding factors, some investigators who examined the effects of prenatal alcohol exposure on externalizing diagnoses in offspring examined the possible mediating role of familial alcoholism. Langbehn and Cadoret¹³ assessed parental diagnosis, and Hill et al¹⁴ assessed familial risk. Langbehn and Cadoret reported that the effect of prenatal alcohol was still significant even after accounting for parental alcoholism, whereas Hill et al found that the effect was no longer significant after accounting for familial alcoholism. It should be noted that Hill et al used an extensive accounting of familial alcoholism diagnoses, including both first- and second-degree relatives, which may have more fully accounted for familial risks. In addition, Hill et al were able to assess alcohol use in pregnancy by direct interviews with mothers. In contrast, Langbehn and Cadoret had to rely on a review of adoption clinic records, which may have focused the sample on particularly heavy drinkers who would be most likely to be recognized. Neither of these studies investigated the role of parental antisocial diagnoses.

The purpose of this investigation was to address the role of both parental substance use diagnoses and parental antisocial diagnoses in the relationship between low levels of prenatal alcohol intake and later offspring CD symptoms. Also addressed was the role of prenatal tobacco exposure. Risk for drinking in pregnancy is often correlated with risk for smoking in pregnancy.^{1,27,28} There is also increasing evidence of an association between prenatal tobacco exposure and later development of offspring externalizing disorders,^{29–32} although this association is similarly confounded by issues already discussed^{33,34}; therefore, we also investigated the role of prenatal nicotine exposure on the association between alcohol exposure and conduct disorder.

METHODS

Participants

Participants in this study were drawn from the Minnesota Twin Family Study (MTFS) and included 674 girls and 578 boys (from 626 same-gender twin pairs, 65.8% monozygotic) and their parents. The MTFS was designed to identify genetic and environmental factors that influence the development of substance abuse and associated psychological disorders. For a full description, see Iacono et al.³⁵ The study used a population-based twin ascertainment method in which all twins who were born in Minnesota were identified by public birth records. Male twins were identified from records for 1972–1978 and female twins from records for 1975–1979. More than 90% of all pairs in which both members were still living were located. Excluded were families in which the twins were adopted or had a disability that precluded complet-

ing our assessment. Of eligible twin families, 17% declined participation. After a description of the study, written informed consent and assent were obtained from parents and twins, respectively. All assessments were conducted when the twins turned age 17 years (mean age: 17.48 years; SD: 0.46). MTFS family demographics approximate those for Minnesota families in the 1990 US Census for urban/rural split (0.66/0.34), mean parental age (42 years), percentage white (98%), and percentage married (85%), indicating that participants were broadly representative of families in Minnesota.³⁶

Mean years of education was 13.7 (SD: 1.9) for mothers and 14.2 (SD: 2.3) for fathers. Mean occupational status, as assessed on the Hollingshead system, was 3.7 (SD: 1.6) for mothers and 3.9 (SD: 1.8) for fathers. The Hollingshead scale runs from 1 (executives) to 7 (unskilled employees), with a code of 4 denoting jobs such as data entry operator and bank teller. Consistent with Minnesota demographics for birth years sampled, the majority (98%) of parents were white. There were no differences on maternal or paternal Hollingshead scores between parents who reported maternal alcohol use in pregnancy and those who did not report use.

Clinical Assessments

All twins and their parents were interviewed separately by different interviewers, who underwent extensive training and had at least a BA in psychology. Both the mother and each twin provided documentation of each youth's CD symptoms. Maternal reports of CD symptoms were obtained by using a modified parent version of the Diagnostic Interview for Children and Adolescents-Revised.³⁷ CD was assessed in twins by using the Structured Clinical Interview for DSM-III-R Personality Disorders.³⁸ *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) was the reigning diagnostic classification system at the time of this assessment.

To assess alcohol dependence, nicotine dependence, and illicit drug disorders in biological parents, we used the expanded substance abuse module of the World Health Organization's Composite International Diagnostic Interview³⁹. Assessment of the DSM-III-R APD criteria was obtained with the Structured Clinical Interview for DSM-III-R Personality Disorders. Adult antisocial behavior (AAB) was additionally assessed; this designation derived from DSM-III-R criteria for APD, which requires the presence of CD before age 15 as well as 4 symptoms of "irresponsible and antisocial behavior since the age of 15." Participants with AAB satisfy the second requirement but do not satisfy the criteria for CD before age 15. Various reports substantiate the construct validity of AAB, showing that its correlates mirror those of APD.^{13,40}

Data from interviews were used to diagnose lifetime DSM-III-R disorders by teams of 2 advanced clinical psychology PhD students who reviewed audiotaped interviews to arrive at a consensus on each clinically significant diagnostic symptom. For adolescents, mother and child reports were independently reviewed, and any CD symptom that was reported by either informant was counted as present. Previous reports showed that each informant contributes valuable information that is not

contributed by other informants.^{41,42} A computer algorithm, based on DSM-III-R, was then used to assign diagnoses. For estimation of the reliability of the consensus process, interviews of >600 individuals from the MTFs were independently reevaluated by a second team. Inter-team agreement, assessed with the κ statistic, was 0.89 or higher for adult diagnoses and 0.75 for CD.

Diagnoses were assigned at 2 levels of certainty: definite (all diagnostic criteria satisfied) and probable (1 symptom short of definite diagnosis). Probable diagnoses were included to help identify lifetime disorder in currently asymptomatic individuals who must rely on memory to recall symptoms. This approach was introduced as part of the Research Diagnostic Criteria to increase diagnostic sensitivity of lifetime diagnoses and is particularly appropriate for nonclinical population samples.⁴³ By using these criteria, 35.8% of the boys ($n = 207$; 79 probable) and 10.4% of the girls ($n = 70$; 46 probable) exhibited enough symptoms to qualify them for definite or probable diagnoses of CD. Significantly more adolescents of mothers who drank during pregnancy (30.5%) received a diagnosis of CD than adolescents whose mothers did not drink during pregnancy (20.9%; $\chi^2 = 4.19$, $P = .04$).

Alcohol dependence (at any point in a lifetime) was diagnosed in 43.0% of fathers and 11.1% of mothers. Rates of paternal and maternal lifetime illicit drug disorder were 15.7% for fathers and 8.8% for mothers. Lifetime nicotine dependence was diagnosed in 52.0% of fathers and 38.8% of mothers. Antisocial spectrum diagnosis (ie, lifetime CD, APD, or AAB) was present in 40.3% of fathers and 9.4% of mothers. When data for 1 parent were missing, only diagnosis-positive cases were included.

Maternal Prenatal Alcohol and Tobacco Use

Maternal prenatal alcohol use was assessed by the following interview questions: "As you know, it was very common in the past for women to drink during pregnancy. During your pregnancy with the twins, how much did you drink during an average week?" Mothers who endorsed ≥ 1 drink per week were coded positive as drinking during pregnancy. Maternal prenatal tobacco use was assessed by the following interview question on the substance abuse module: "During your pregnancy with the twins, how much did you usually smoke/use tobacco per day?"

Statistical Analyses

The number of DSM-III-R CD symptoms was chosen as the outcome variable, rather than categorical diagnosis, for several reasons. First, there is ample evidence supporting the dimensional nature of CD⁴⁴⁻⁴⁶ and the construct validity of measuring this dimension by using CD symptom counts.^{47,48} Second, symptom counts provide increased statistical power, especially important in a community-based sample in which CD rates are lower than in clinical samples. To reduce skewness, we log-transformed the symptom count.

In all analyses, data were clustered within twin pairs to account for nonindependence. This was done by using

generalized estimating equations⁴⁹ in PROC GENMOD and PROC MIXED, procedures in the SAS package. First, we used logistic regression (in PROC GENMOD) to test the extent to which characteristics of families, specifically children's gender, rates of mothers' and fathers' psychopathology, and maternal smoking during pregnancy, differed by maternal alcohol use groups. Second, we used multiple regression (in PROC MIXED) to test the effect of prenatal alcohol exposure on offspring CD symptoms and in separate models included covariates that are likely associated with mothers' use of alcohol during pregnancy as well as with CD symptoms in offspring. To determine whether the effect of prenatal alcohol exposure remained once parental psychopathology and prenatal nicotine exposure were statistically controlled, we fit 3 separate regression models. The base model included prenatal alcohol exposure (yes/no), offspring gender, and their interaction, with the last included because the symptom counts varied by gender. The parental psychopathology model examined whether prenatal alcohol exposure predicted adolescent CD after adjusting for parental DSM-III-R diagnosis (either parent affected) of alcohol dependence, illicit drug disorder, and antisocial spectrum diagnosis. This model also included all of the terms of the base model. The prenatal nicotine exposure model examined the effect of prenatal alcohol exposure after accounting for the possible contribution of maternal smoking in addition to all of the other variables in the first 2 models.

RESULTS

Eighty-two (13.1%) of 626 mothers reported drinking during pregnancy, averaging 2.9 (SD: 3.1) drinks per week. Mean non-log-transformed symptom counts for CD were 1.95 (SD: 2.35) for boys with prenatal alcohol exposure ($n = 92$) versus 1.42 (SD: 1.75) for boys without prenatal alcohol exposure ($n = 486$). For girls, the mean symptom count for CD was 0.74 (SD: 0.93) for those with prenatal alcohol exposure ($n = 72$) versus 0.42 (SD: 0.96) for those without prenatal alcohol exposure ($n = 602$). There were no significant differences between pregnancy drinkers and nondrinkers on length of gestation in weeks (nondrinkers: 38.0 [SD: 6.09]; drinkers: 37.7 [SD: 3.21]; $\chi^2 = 0.78$, $P = .38$) or in offspring birth weight in ounces (nondrinkers: 92.7 [SD: 19.5]; drinkers: 88.8 [SD: 19.3]; $\chi^2 = 2.91$, $P = .09$).

Characteristics of families by maternal alcohol use groups are presented in Table 1. Families in which the offspring were exposed to maternal alcohol use during pregnancy generally had higher rates of maternal and paternal externalizing psychopathology, although only a few of these differences were significant at $P < .05$. Families with maternal prenatal alcohol use had higher rates of maternal alcohol dependence, maternal nicotine dependence, and maternal smoking during pregnancy; however, only a small proportion (20.7%) of the women who used alcohol in pregnancy were judged to have a lifetime diagnosis of alcohol dependence. Mothers who drank prenatally were more than twice as likely (32.4% vs 15.5%) to smoke during pregnancy than nondrinking

TABLE 1 Comparison of Families With Mothers Who Used Alcohol During Pregnancy With Families With Mothers Who Did Not

Family Characteristic	% of Family Characteristics According to Maternal Prenatal Alcohol Use Groups		Statistical Tests for Differences According to Maternal Prenatal Alcohol Use Groups	
	Yes (<i>n</i> = 1088)	No (<i>n</i> = 164)	χ^2	<i>P</i>
Offspring, % female	55.3	43.9	3.65	.06
Maternal alcohol dependence	9.6	20.7	5.48	.02
Paternal alcohol dependence	41.4	52.7	3.28	.07
Maternal illicit drug abuse/dependence	7.9	14.6	2.65	.10
Paternal illicit drug abuse/dependence	15.0	20.3	1.31	.29
Maternal nicotine dependence	35.5	60.9	16.57	<.001
Paternal nicotine dependence	51.1	58.2	1.25	.26
Maternal antisocial diagnosis	10.1	4.9	3.61	.06
Paternal antisocial diagnosis	39.5	45.9	1.08	.30
Maternal smoking in pregnancy	18.8	47.6	20.30	<.001

Sample *n* reflect the numbers of offspring; Number of mothers in each group is *N*/2 because *N* represents the number of twins in each group.

mothers, reporting an average number of 13.8 (SD: 9.5) cigarettes per day.

Table 2 presents the results of the 3 regression models, with the first 2 columns indicating the effects for the base model in the absence of covariates. Results for the base model indicate that, as expected, male gender and prenatal alcohol exposure were associated with higher levels of CD symptoms. The interaction between gender and prenatal alcohol exposure was not significant. In the parental psychopathology model, parental substance use and antisocial disorders were added as covariates. Although many of the parental disorders significantly predicted offspring CD symptoms, the effect of prenatal alcohol exposure remained statistically significant. The

prenatal nicotine exposure model, which accounted for mother's smoking during pregnancy and all of the other covariates, similarly showed that the effect of prenatal alcohol exposure remained significant. In other words, all 3 models consistently found that after accounting for the effects of important possible confounds, prenatal alcohol exposure was associated with elevated levels of offspring CD symptom counts. Drinking alcohol during pregnancy had a significant, independent impact on the prediction of offspring CD, even after the impact of parental alcoholism, illicit drug disorder, antisocial personality, and pregnancy smoking were taken into account.

Because other factors in addition to parental substance use and antisocial personality might affect the likelihood of offspring CD outcomes, we reran these analyses while adjusting for monozygosity, gestational age, and birth weight. When these factors were included as simultaneous, additional covariates, the effects of prenatal alcohol exposure on CD symptoms remained significant.

DISCUSSION

In this report, we showed that drinking during pregnancy plays a strong and significant role on offspring development. Prenatal alcohol exposure raised rates of offspring CD symptoms in this population sample, even after the effects of parental alcoholism, parental drug abuse/dependence, and externalizing disorders had been taken into account. We arrived at these results by using a sophisticated statistical technique, hierarchical linear modeling, which corrected for the correlated observations found in twin samples and also adjusted for potentially confounding covariates, including parental psychopathology and prenatal nicotine exposure. We were also able to demonstrate that these differences were not accounted for by zygoty, gestational age, or birth weight.

We chose to focus on rates of CD symptoms, rather than diagnoses, to strengthen the statistical power needed to make multiple statistical adjustments for potentially confounding effects, as well as to take into account the nonclinical nature of our sample; however, analyses that used diagnoses of CD in adolescents and diagnoses of alcoholism in mothers suggested similar

TABLE 2 Effect of Maternal Alcohol Use in Pregnancy and Related Variables on CD in Offspring

Parameter	Base Model (<i>df</i> = 622)		Parental Psychopathology Model (<i>df</i> = 542)		Prenatal Nicotine Exposure Model (<i>df</i> = 541)	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Parental psychopathology						
Alcohol dependence			26.26	<.001	26.27	<.001
Nicotine dependence			11.16	<.001	11.17	<.001
Illicit substance abuse/dependence			9.44	.002	9.45	.002
Antisocial/behavioral disorder			1.87	.17	1.87	.17
Prenatal nicotine exposure					0.22	.64
Gender	134.04	<.001	139.72	<.001	139.78	<.001
Prenatal alcohol exposure ^a	10.62	.001	10.57	.001	11.59	<.001
Gender X prenatal alcohol exposure	0.11	.740	0.00	.950	0.00	.98

df indicates degree of freedom.

^a Primary finding of interest indicating the effect of maternal alcohol consumption on offspring CD symptoms (base model), the same effect after adjusting for parental psychopathology, and this effect after adjusting for parental psychopathology and prenatal nicotine exposure.

patterns. When mothers who had lifetime diagnoses of alcoholism ($n = 69$) were divided into those who reported drinking while pregnant ($n = 17$) and those who did not ($n = 69$), rates of CD in offspring were higher among the pregnancy drinkers (44.1% of whose offspring had CD) in contrast to the nonpregnancy drinkers (20.2%; $P < .05$), corroborating our finding that the alcohol exposure played a unique role.

These findings build on previous literature that reported this relationship by using questionnaire-based outcome measures.^{3,10,12,50} It is also consistent with reports of CD and CD-related behaviors in FAS samples, such as studies by Streissguth et al,⁵¹ which have yielded results that are suggestive of increased rates of CD. Moreover, these findings are congruent with recent work suggesting that even low levels of alcohol exposure in pregnancy can be harmful.^{11,52,53} In this general population sample, reporting a very low average alcohol consumption of just 3 drinks per week in pregnancy, adverse developmental outcomes were still observed.

One methodologic limitation is the 17-year period between pregnancy and the interviews for this study. This is longer than most studies and raises the concern of underreporting of alcohol use in pregnancy; however, some previous reports suggested that accuracy of reporting (as indexed by correlations with alcohol-related physical anomalies) may be increased by gathering reports of mothers' pregnancy alcohol use 1 to 10 years after birth, when presumably anxiety about pregnancy behaviors has subsided.^{54–56} Concern about the effects of this time lapse on our reports on pregnancy drinking behaviors is also mitigated by the significance of the finding for the relationship between prenatal drinking and CD. One would expect that the effect of the 17-year time lapse in reporting would have decreased the possibility of finding any effect, with mothers misreporting their drinking that long ago. Instead, the significance of the effect seems to be strong enough to have overpowered any tendency of mothers to downplay or forget their history of pregnancy drinking.

An additional consideration relates to our use of a twin sample. Twins are known to receive less uteroplacental blood flow per twin compared with singletons and to have increased likelihood of preterm birth and lower average birth weights.⁵⁷ It is possible that some of the unique characteristics of being a twin could have interacted with the alcohol exposure to affect our findings. Thus, replication of our results in a nontwin sample is important.

CONCLUSIONS

Results of this investigation indicate that prenatal alcohol exposure may play a significant role in the prediction of risk for CD, separate from postnatal environmental and genetic risk factors that are likely to be associated with antisocial and alcoholic parents. Although the role of additional confounding variables cannot be conclusively ruled out by this inherently correlational design, these results suggest the importance of prevention programs directed at reducing even small amounts of alcohol consumption in pregnancy.

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